UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: March 22, 2016

SUBJECT: **Isothiazolone:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of December 3, 2015: Recommendations on the Immunotoxicity Study

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THROUGH: Jeff Dawson, Co-Chair
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TO: Jonathan Chen, Ph.D., Toxicologist
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MEETING ATTENDEES:

HASPOC Members: Elissa Reaves, Elizabeth Mendez, Jaime D'Agostino, Jeffrey Dawson, John Kough, Jonathan Leshin, Matt Lloyd, Ray Kent, Sarah Gallagher, Uma Habiba

Presenter: Jonathan Chen

Other Attendees: Anwar Dunbar, Lata Venkateshwara, Matthew Crowley

I. PURPOSE OF MEETING

The isothiazolone biocides are a class of chemicals commonly used as material preservatives in antimicrobial pesticide products. There are six registered isothiazolone biocides and one new isothiazolone biocide currently undergoing evaluation for registration. These chemicals are presented below.

1) 5-Chloro-2-methyl-4-isothiazolin-3-one (CMIT)/ 2-methyl-4-isothiazolin-3-one (MIT) mixed in a 3:1 ratio
2) 2-methyl-4-isothiazolin-3-one (MIT) as a single active ingredient
3) 4,5-Dichloro-2-n-octyl-4-isothiazoln-2-one (DCOIT)
4) 2-n-Octyl-4-isothiazolin-3-one (OIT)
5) 1,2-Benzisothiazolin-3-on (BIT)
6) 1,2-Benzisothiazolin-3-one, 2-butyl (BBIT)
7) 1,2-Benzisothiazolin 3-one,2-methyl (Methyl-BIT or mBIT); not currently registered.

Based on the current 40 CFR Part 158W Toxicology Data Requirements, immunotoxicity study is required for each of the isothiazolone chemicals. The Hazard and Science Policy Council (HASPOC) met on December 3, 2015 to discuss the need for these studies to support the thidiazuron registered uses.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT

The isothiazolone biocides are a class of chemicals commonly used as material preservatives in antimicrobial pesticide products for the control of bacteria, fungi, and/or algae. These pesticide products can be used in/on countertops/utensils (food use), pulp and paper (food packaging), vinyl flooring, household cleaning products, laundry detergent, metalworking fluids, paint (in-can preservative, including paint for ship hulls), plastics, textiles/carpets and wood (pressure treatment).

III. TOXICITY OF ISOTHIAZOLONE CHEMICALS

The available information for all the isothiazolone chemicals were presented to the Toxicology Science Advisory Council (ToxSAC), on May 21, 2015 meeting, TOXSAC concluded that it is appropriate to bridge the chemicals into one group based on the similarity of the toxicology profiles. All the effects through all different routes of exposure (oral, dermal and inhalation) are point of contact irritation-like effects. The primary effects through oral route are irritation-like effects in the upper GI tract, including stomach lesions, irritation, hyperplasia/ hyperkeratosis of the squamous epithelium of the forestomach, etc. Through dermal route, skin irritation including hyperkeratosis, acanthosis, hyperplasia and inflammation, etc. are the primary concern. In the available inhalation studies, the primary effects are histopathological alterations observed in nose, larynx, and lungs.

ToxSAC concluded that for risk assessment purposes, chemical-specific data should be used when available. When chemical-specific data are not available, the most conservative endpoint for which there is data from other isothiazolones should be used.

IV. STUDY WAIVER REQUESTS

1. Immunotoxicity Study

Immunotoxicity studies are required in the 2013 revised 40 CFR Part 158W "Data Requirements for Antimicrobial Pesticides" for all antimicrobial pesticides. However, since all the effects noticed in existing database are point of contact irritation-like effects. No evidence of immune-suppression effects been noticed in isothiazolone related database.
Although dermal sensitization studies indicating all isothiazolone chemicals are dermal sensitizers, it is not related to the immunotoxicity study design which is focusing on immune-suppression effects of the testing chemicals.

a. Indicators for Potential Immunotoxicity

There are some potential immunotoxicity indicators noticed in the data matrix. For example, increased WBC in the 90-day rat oral gavage study for BIT (MRID 46346201), decreased thymus weight in 90-day dog oral study (MRID 45747201), decreased spleen and/or thymus weight in 2-generation reproductive studies for DCOIT (MRID 45756501) and B-BIT (MRID 48261201). However, these effects are happened only happened at high dosed animals, or happened in animal with significant body weigh change and there was no consistent compelling effects across the individual chemical databases. Therefore, these potential immunotoxicity indicator are likely secondary effects to the primary concerned point of contact irritation-like effects.

Parameter	Findings
Hematology Indicators (WBC changes)	90-d rat gavage study for BIT (MRID 46346201) ↑ in WBC
Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	90-day dog oral study for DCOIT(MRID 45747201) Decreased thymus weight accompanied by diffuse atrophy of the cortical and medullary lymphoid area of the thymus. 2-generation rat reproductive Study for DCOIT (MRID 45756501) Decreased thymus and spleen weights in F1 and F2 offspring were observed, but there was no corresponding histopathology of the organs. 2-generation rat reproductive Study for B-BIT (MRID 48261201) Decreased spleen weights in the offspring animals

Histopathology Indicators (Spleen, Thymus, Lymph nodes)	See above
Toxicity Profile	Point of contact irritation-like effects

b. Evidence for Immunotoxicity for SAR Chemicals –Retrospective Analysis:

In considering the need for an immunotoxicity toxicity study, the Agency will evaluate other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential immunotoxic effects. Specifically, if other similar pesticides show immunotoxicity studies to be more sensitive, an immunotoxicity study may be required, depending on the exposure profile. There is no immunotoxicity study available for the chemical family.

V. HASPOC CONCLUSIONS

Based on a WOE approach, considering all of the available hazard and exposure information, HASPOC concludes that the immunotoxicity study is not required at this time for isothiazolone based on 1) the lack of consistent evidence for immunotoxicity in the toxicity databases of the chemical class and 2) the primary toxicity of these chemicals are point of contact irritation.